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NOVEL BENZOTHIAZEPINES AND USES THEREOF

Field of the invention

The present invention relates to novel benzothiazepines, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of various diseases especially Alzheimer's disease and other diseases relating to the deposition of amyloid.

Background of the invention

Alzheimer's Disease (AD) is a progressive, neurodegenerative disease characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotionally stability. AD is a common cause of dementia in humans and a leading cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major public health problem throughout the world. No treatment that effectively prevents AD or reverses the clinical symptoms and underlying pathophysiology is currently available and the disease is currently considered among experts to be incurable.

The histopathological manifestations of AD are characteristic lesions known as amyloid (or senile) plaques and neurofibrillar tangles that are found in the regions of the brain associated with memory, reasoning and cognition. Similar alterations are observed in patients with Trisomy 21 (Down's syndrome) and hereditary cerebral hemorrhage with amyloidosis of the Dutch-type.

The major constituent of amyloid plaques is amyloid β protein. Amyloid β protein is derived from the proteolytic cleavage of amyloid precursor protein (APP). Processing of APP to amyloid β protein and other APP fragments is governed by a group of enzymes known as secretases. One type of secretase, γ-secretase, is responsible for the protein cleavage that produces amyloid β protein. Compounds that inhibit either β or γ secretase activity, either directly or indirectly would reduce the production of amyloid β protein resulting in the treatment or prevention of disorders associated with amyloid β protein. Thus there is a continuing need for compounds that inhibit amyloid β protein production. The present

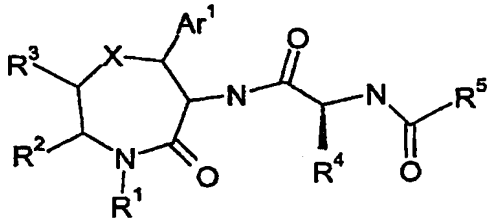
invention meets this and related needs by providing a family of novel compounds and related methods of use.

Summary of the invention

In accordance with the present invention, the applicants have hereby discovered novel compounds that inhibit γ secretase and thereby inhibit the production of amyloid β protein. The invention includes pharmaceutically acceptable salts or prodrugs of such compounds. Also in accordance with the present invention applicants provide pharmaceutical compositions and a method to use invention compounds in the treatment of degenerative neurological disorders.

Detailed description of the invention

Provided herein are novel compounds of structural diagram (I):



wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 2 sulfur atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, 2 or 3 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5 or 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or substituted phenyl with 0, 1, 2, or 3 R^e;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, C_{1-3}alkoxy, or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, aryl, or heteroaryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, SH, CH_2SCH_3, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, 2 or 3 R^e;

R^{10} is alkyl or R^9;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, or NR^aR^b;

R^e is, at each occurrence independently selected from OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-3}alkyl, or C_{1-3}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, or aryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_{1-3}alkyl, or C_{1-3}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^e is, at each occurrence independently selected from H, C_{1-3}alkyl, phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl or aryl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, NO_2, F, Cl, Br, I, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, or 1 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3, C_{1-6}alkyl;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, or 2 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, NO_2, CF_3, or C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from C_{1-6}alkyl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

Ar^1 is a 6-membered aromatic or heteroaromatic ring having 0, or 1 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CF_3;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, or CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, or OH;

R^9 is phenyl substituted with 2 R^e;

R^{10} is R^9;

Another embodiment of the invention occurs wherein X is C, O, SO_2 or S.

Another embodiment of the invention occurs wherein:

Ar^1 is a 5-or 6-membered aromatic or heteroaromatic ring optionally substituted with 0 or 1 R^e said ring having 1 nitrogen, oxygen or sulfur atom.

Another embodiment of the invention occurs wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b.

Another embodiment of the invention occurs wherein:

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl.

Another embodiment of the invention occurs wherein:

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f.

Another embodiment of the invention occurs wherein:

R^e is, at each occurrence independently selected from F or Cl.

Another embodiment of the invention occurs wherein R^f is F or Cl.

Another embodiment of the invention occurs wherein R^4 is H or CHR^7R^8.

Another embodiment of the invention occurs wherein R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$.

Another embodiment of the invention occurs wherein:

R^7 and R^8 are, at each occurrence independently selected from H or OH.

Another embodiment of the invention occurs wherein R^9 is phenyl substituted with 2 R^e.

Another embodiment of the invention occurs wherein R^{10} is phenyl substituted with 2 R^e.

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b;

R^a and R^b are, at each occurrence independently selected from H,or C_{1-4}alkyl;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0,1 or 2 R^f;

R^e is, at each occurrence F;

R^f is F or Cl;

R^4 is H, or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H or OH;

R^9 is phenyl 3, 5-disubstituted with F;

R^{10} is phenyl 3, 5-disubstituted with F.

In a further embodiment the present invention provides a compound selected from:

(2S)-N-[(2S,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2S,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2R,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N-[(2*S*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

N-[(2*R*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

or a pharmaceutical acceptable salt thereof.

The use of a compound as defined herein, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with β-amyloid production, Alzheimer's disease, or Down's Syndrome.

A method for the treatment of neurological disorders associated with β-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as defined herein.

A method for inhibiting γ-secretase activity comprising administering to a host in need of such inhibition a therapeutically effective amount of a compound as defined herein that inhibits γ-secretase activity.

A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising administering a therapeutically effective amount of a compound as defined herein.

A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt as defined herein.

A pharmaceutical composition comprising a compound of formula (I), as defined herein, together with at least on pharmaceutically acceptable carrier, diluent or excipent.

Definitions

The definitions set forth in this section are intended to clarify terms used throughout this application. The term "herein" means the entire application.

As used in this application, the term "substituted," as used herein, means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. For example when a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^1, R^7, R^a, R^e etc.) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^1, then said group may optionally be substituted with 0,1, 2 or 3 R^1 groups and R^e at each occurrence is selected independently from the definition of R^e. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein "acyl" refers to radicals of the of the general formula –C(=O)-R, wherein R is hydrogen, hydrocarbyl radical, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

As used herein "aromatic" refers to hydrocarbyl radicals having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising up to about 14 carbon atoms.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

As used herein, "alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more unsaturated carbon-carbon bonds that may occur at any stable point along the chain. Examples of "C_{3-6}alkenyl" include, but are not limited to, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, hexenyl, and the like.

As used herein, "alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more carbon-carbon triple bonds that may occur at any stable point along the chain, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "aryl" is intended to mean aromatic radicals including both monocyclic aromatic radicals comprising 6 carbon atoms and polycyclic aromatic radicals comprising up to about 14 carbon atoms.

As used herein, "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, bicyclooctane, bicyclononane, bicyclodecane (decalin), bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein "cycloalkenyl refers to ring-containing radicals having at least one carbon-carbon double bond in the ring, and having in the range about 3 up to 12 carbons atoms.

As used herein "cycloalkynyl" refers to ring-containing radicals having at least one carbon-carbon triple bond in the ring, and having in the range about 3 up to 12 carbons atoms.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, heptafluoropropyl, and heptachloropropyl. "Haloalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge; for example trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like. "Halothioalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "heterocycle" or "heterocyclic" refersto a ring-containing monovalent and divalent radicals having one or more heteroatoms, independently selected from N, O and S, as part of the ring structure and comprising at least 3 and up to about 20 atoms in the rings. Heterocyclic groups may be saturated or unsaturated, containg one or more double bonds, and heterocyclic groups may contain more that one ring. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocycle may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azetidine, aziridine, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidine, pyrroline, pyrrolidine, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, thiophane, thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl,

thienooxazolyl, thienoimidazolyl, thiophenyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers that release the active parent drug according to formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Formulation

Compounds of formula I according to the present invention may be administered orally, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

Preferred routes of administration are orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

An effective amount of a compound of formula I of the present invention for use in therapy of Alzheimer's Disease is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the cognitive symptoms, to slow the progression of worsening cognitive symptoms, or to reduce in patients with cognitive symptoms the risk of getting worse (progressing to dementia or worsening the present degree of dementia).

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers include magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Salts include, but are not limited to, pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts of compounds of the present invention include: acetate, bicarbonate, carbonate, hydrobromide, hydrochloride, phosphate/diphosphate, sulfate, choline, diethanolamine, ethylenediamine, meglumine, aluminum, calcium, magnesium, potassium and sodium. Examples of pharmaceutically unacceptable salts of compounds of the present invention include: hydroiodide, perchlorate, tetrafluoroborate, lithium.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for

oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

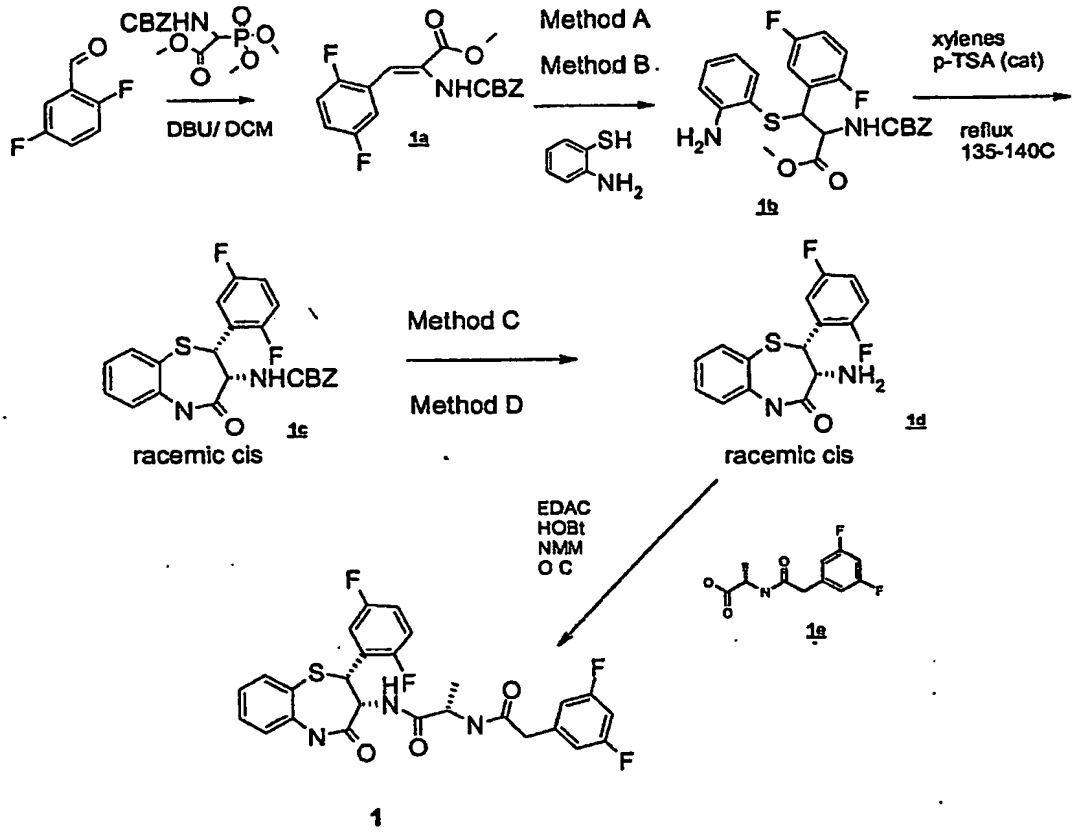
The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

Examples

Chemical abbreviations used in the Examples are defined as follows: "EtOAc" denotes ethyl Acetate; "DMF" denotes dimethylformamide; "DCM" denotes dichloromethane; "HOBt" denotes hydroxybenzotriazole; "EDAC" denotes 1-Ethyl-3(dimethylaminopropyl)carbodiimide; "p-TSA" denotes p-toluenesulfonic acid; "DBU" denotes 1,8-Diazabicyclo[5.4.0]undec-7-ene; "NMM" denotes N-Methylmorpholine; "CBZ" denotes carbobenzyloxy; "TBAB" denotes Tetrabutylammonium bromide; "Min." denotes minutes; "H" denotes hours; "RT" denotes room temperature.

LC/MS HPLC method: Agilent Zorbax 5µ SB-C8 column 2.1mm x 5 cm. Solvents: A = H_2O with 0.05% TFA, B =10% H_2O, 90% Acetonitrile, 0.05% TFA. Gradient: (10-90%B over 3 Min., 90% B hold thru 4 Min., -10% B at 5 Min. and hold at 10% B until 6 Min).

Example 1



Example 1. N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2*R*,3*R*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide (1)

To a solution of racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (1d) (300mg) in DCM (40mL) at 0°C under N_2 was added *N*-[(3,5-difluorophenyl)acetyl]-L-alanine (1e) (238 mg), HOBt-hydrate (330 mg), EDAC.HCl (282 mg) and N-methyl morpholine (165 mg). The reaction mixture was stirred 1 H at 0°C, concentrated in vacuo and partitioned between H_2O (100mL) and EtOAc (125mL). The organic phase was collected and consecutively washed with H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered and evaporated to yield a mixture of the title compound and N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2*S*,3*S*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide. The crude product (500 mg) was purified by flash chromatography (50%EtOAc/hexanes) to afford the title compound (180mg, 69%) as an off-

white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H), 3.48 (s, 2H), 4.29 (p, 1H), 4.93 (t, 1H), 5.68 (d, 1H), 6.01 (d, 1H), 6.50 (d, 1H), 6.73-6.80 (m, 3H), 6.93-7.02 (m, 2H), 7.15 (d, 1H), 7.30 (t, 1H), 7.43 (t, 1H), 7.5-7.6 (m, 1H), 7.73 (d, 1H), 7.74 (s, 1H). MS APCI, m/z = 532(M^+). LC/MS 2.53 min., Method A.

The starting amine, racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (1d), was prepared in the following manner:

Methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate. A stirred solution of N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (6.1 g) and 2,5-difluorobenzaldehyde (2.0 g) in dry DCM (60 mL), was treated dropwise with a solution of DBU (2.5mL) in DCM (20 mL). The mixture was stirred at room temperature for 2h, then was concentrated to approximately 20 mL and partitioned between ethyl acetate (150 mL) and 1N hydrochloric acid (50 mL). The organic extract was collected, consecutively washed with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and brine, dried (Na_2SO_4), filtered and evaporated. The crude product (6.5g) was purified by flash chromatography (20%EtOAc/hexanes) to yield the title compound (4.0g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.10, (s, 2H), 6.60 (bs, 1H), 6.9-7.1 (m, 2H), 7.21 (m, 1H), 7.2-7.3 (m, 6H). MS APCI, m/z = 348(M^+). LC/MS 2.53 min (Method A).

b. Methyl β-[(2-aminophenyl)thio]-*N*-[(benzyloxy)carbonyl]-2,5-difluorophenylalaninate (1b).

Method A

To an ice-cooled solution of sodium methoxide (760 mg) in anhydrous methanol (20 mL) under N_2 (vacuum degassed 3x with nitrogen) was added 2-aminothiophenol (1.7 g). The reaction mixture stirred at 0° C for 10 min and then a solution of methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate (2.32 g) in methanol (10 mL) was added. The reaction mixture was heated to reflux for 2h and then was cooled to room temperature and stirred overnight. The reaction mixture was concentrated to ca. 10 mL, then was partitioned between cold 1N hydrochloric acid (75 mL) and ethyl acetate (125 mL). The organic phase was separated and consecutively washed with 1N hydrochloric acid (4x), dilute aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered and evaporated. The title compound was isolated as the hydrochloride salt. (3.0g, 88 %, 2:1 Z:E). ^{1}H NMR (300

MHz, d6-DMSO) δ 3.4 (s, 2H), 3.7 (s, 1H), 4.6–5.1 (m, 7H), 6.3 (t, 0.67H), 6.4 (t, 0.33H), 6.7-7.4 (m, 10H), 8.1 (d, 0.33H),), 8.4 (d, 0.67H). MS APCI, m/z = 473(M^+). LC/MS 2.78 min.

Method B

To an ice-cooled solution of 2-aminothiophenol (8.7g) in anhydrous methanol under N_2 (vacuum degassed 3x with nitrogen) was added methyl (2*Z*)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate (3.46 g) followed by triethylamine (975uL). The reaction mixture was stirred at room temperature for 4 days, then was reduced in vacuo to near dryness. The mixture was partitioned between cold 1N hydrochloric acid (75 mL) and ethyl acetate (125 mL). The organic phase was separated and consecutively washed with 1N hydrochloric acid (4x), dilute aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered and evaporated to yield 5.8 g of an oil. Purification by flash chromatography (25 % EtOAc/hexanes) afforded the title compound (4.3g, 65%) Z:E ratio of 82:18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 2.4H), 3.71 (s, 0.6H), 4.28 (s, 1.6H), 4.72 (s, 0.4H, 4.8–5.1 (m, 4H), 5.3 (d, 0.2H), 5.86 (d, 0.8H), 6.58 (t, 0.8H), 6.68 (d, 0.8H), 6.9-7.4 (m, 8H). MS APCI, m/z = 473(M^+). LC/MS 2.78 min.

c. **Benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (1c).**

A suspension of methyl β-[(2-aminophenyl)thio]-*N*-[(benzyloxy)carbonyl]-2,5-difluorophenylalaninate (4:1, Z:E) (4.3 g) and p-toluenesulfonic acid (catalytic) in xylenes (100 mL) was heated to reflux for 2 h, using a Dean-Stark apparatus to remove water. The mixture was then cooled, resulting in precipitation of the crude product as a white solid (3.3 g, 4:1, cis:trans). This was recrystallized from ethyl acetate/ether to afford the title compound (2.4 g, 60 %). ^{1}H NMR (300 MHz, d6-DMSO) δ 4.63 (t, 1H), 4.96 (s, 2H), 5.47 (d, 1H), 7.00 (d, 1H), 7.23–7.34, (m, 9H), 7.49-7.53 (m, 2H), 7.70 (d, 1H), 10.57 (s, 1H). MS APCI, m/z = 441(M^+). LC/MS 2.74 Min

d. ***cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (1d)**

Method C

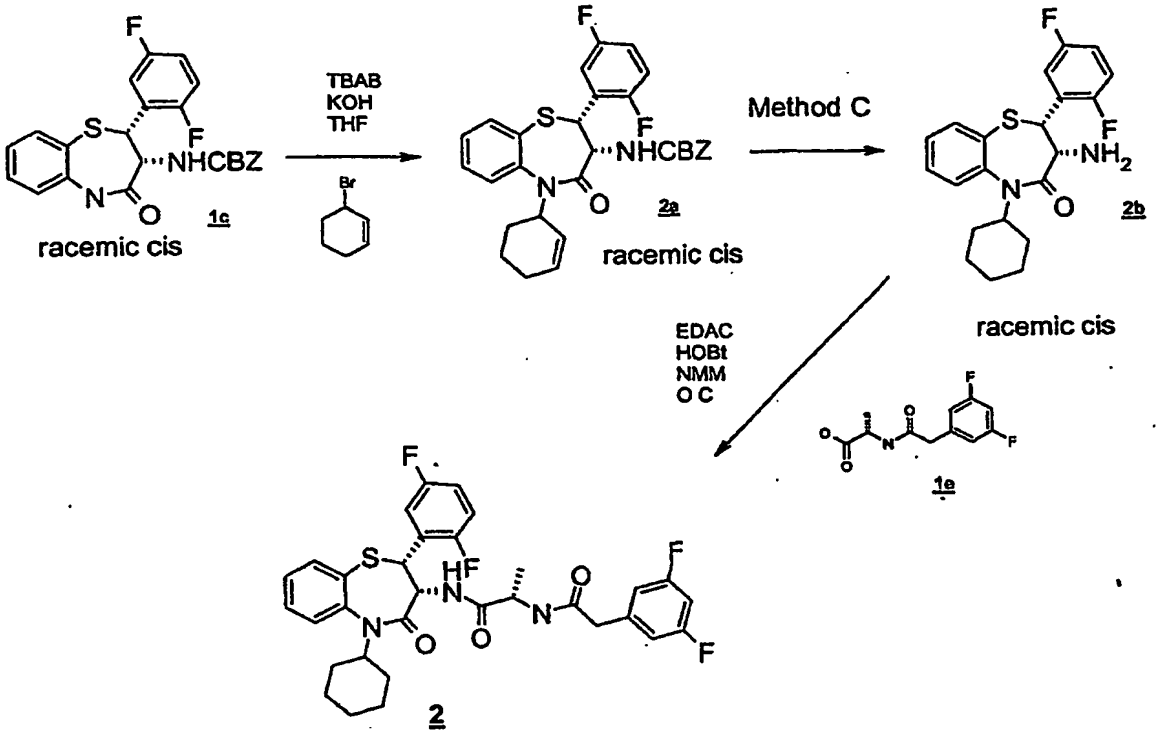
A mixture of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (1.7 g) and 10% Pd/C (1.7 g, DeGussa type 50%wt H_2O) in glacial acetic acid (80 mL) was hydrogenated at 50 psi H_2 for 3h. The reaction mixture was filtered through

Celite and concentrated in vacuo. The crude oil was triturated with ether to yield a white solid (1.3g). The solid was partitioned between ethyl acetate and dilute ammonium hydroxide. The organic phase was separated and consecutively washed with dilute ammonium hydroxide and brine, dried (Na_2SO_4) and evaporated. The residue was treated with saturated HCl(g) in ethyl aceate/ether to provide the hydrochloride salt of the title compound as a white solid (1.1g, 90%). ^{1}H NMR (300 MHz, d6-DMSO) δ 4.33 (d, 1H, J=7 Hz), 5.6 (d, 1H, J=7 Hz), 7.13–7.38 (m, 4H), 7.48-7.60 (m, 2H), 7.72, (d, 1H), 8.4 (bs, 3H), 11.0 (s, 1H). MS APCI, m/z = 307(M^+). LC/MS 1.65 Min.

Method D

To benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (0.9 g) was added 30 % HBr/HOAc (5mL). The stirred suspension became a homogeneous solution over 20 min. The reaction stirred at room temperature for an additional 50 min, then was diluted with ether to afford the hydrobromide salt of the title compound (0.75g, 95%). The solid was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated and consecutively washed with dilute aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered and evaporated. The resulting oil was treated with saturated HCl(g) in ethyl aceate/ether to provide the hydrochloride salt of the title compound as a white solid (0.60 g, 85%). This material was indistinguishable to that obtained by Method C.

Example 2. (2)



Example 2. ***N*^{1}-[(2,3-*cis*)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-*N*^{2}-[(3,5-difluorophenyl)acetyl]-L-alaninamide (2).**

Using a procedure similar to that described in Example 1, except using (2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**2b**) (85mg) as the amine component, the title compound (**2**) was obtained as a white solid (20 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0-2.1 (m, 13H), 3.47(s, 2H), 4.2 (p, 1H), 4.45 (m, 1H), 4.64 (t, 1H), 5.44 (d, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 6.73-6.80 (m, 3H), 6.85-6.95 (m, 2H), 7.35-7.49 (m, 4H), 7.75 (d, 1H). MS APCI, m/z = 614(M^+). LC/MS 3.44 Min.

The amine component, (2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**2b**) was prepared in the following manner:

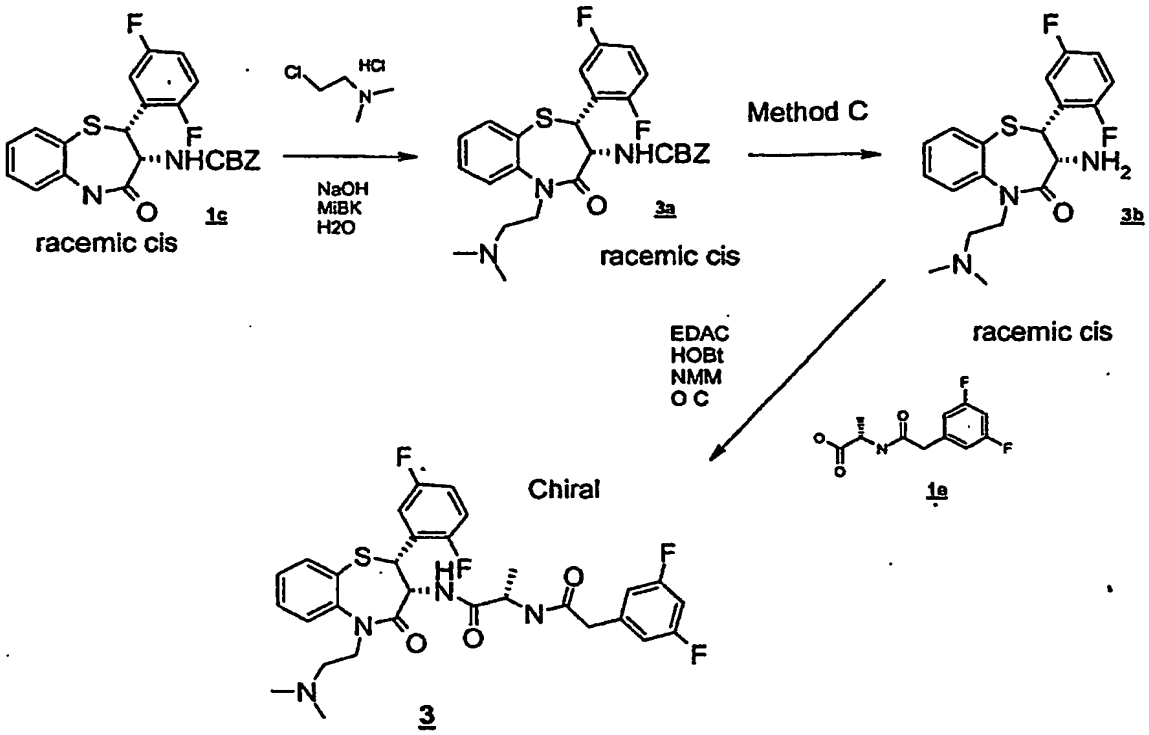
a. **Benzyl (2,3-*cis*)-5-(2-cyclohexen-1-yl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 2a**

To a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate **1c** (150 mg,), prepared as described in Example 1, part c, in THF (10 mL) under N_2 was added powdered potassium hydroxide (25 mg), tetrabutylammonium bromide (11 mg) and 1-bromo-2-cyclohexene (40µl). The reaction mixture was stirred at RT overnight, then was partitioned between water and ethyl acetate. The organic phase was separated and consecutively washed with water and brine, dried (Na_2SO_4), filtered and evaporated to yield the title compound **2a** (175 mg, 98%). This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5-2.3 (m, 6H), 4.6 (t, 1H), 5.0 (d, 2H), 5.2–5.5,(m, 3H), 5.7 (m, 1H), 5.9 (m, 1H), 6.9 (m, 2H), 7.2-7.3 (m, 6H), 7.4 (m, 3H), 7.73 (d, 1H).. MS APCI, m/z = 521(M^+). LC/MS 3.63 Min

b. **(2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2b).**

Using a method similar to that described in Example 1, part d (Method C), benzyl (2,3-*cis*)-5-(2-cyclohexen-1-yl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate **2a** (90mg) was converted to crude **2b**. The crude product purified by flash chromatography (2%MeOH, 1% $NH_4OH/CHCl_3$) to yield **2b** (45mg, 67%), converted to HCl salt (EtOH/ether/HCl). ^{1}H NMR (300 MHz, d6-DMSO) δ1.0-2.1 (m, 10H), 4.11(d, 1H), 4.35 (m, 1H), 5.38 (d, 1H), 7.35 (t, 2H), 7.4–7.5 (m, 2H), 7.6-7.7 (m, 2H), 7.81, (d, 1H), 8.29 (bs, 3H). MS APCI, m/z = 389(M^+). LC/MS 2.57 Min.

Example 3. (3)



Example 3. N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide (3)

Using a procedure similar to that described in Example 1, except using racemic (2,3-*cis*)-3-amino-2-(2,5-difluorophenyl)-5-(2-dimethylamino)ethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b) (100 mg) as the amine component, the title compound (3) was obtained as a white solid (37 mg, 46%). ^{1}H NMR (300 MHz, d6-DMSO) δ1.2 (3H), δ2.3(s, 6H), δ2.35 (m, 1H), δ2.6,(m, 1H), δ3.48 (s, 2H),), δ3.55 (m, 1H),), δ4.22 (p, 1H),), δ4.65 (m, 1H), δ4.77 (t, 1H),), δ5.53 (d, 1H),), δ5.95 (d, 1H),), δ6.36 (d, 1H), δ6.7–7.0 (m, 5H), δ7.27–7.35 (t, 1H), δ7.38 (d, 1H), δ7.48, (t, 1H), δ7.71 (d, 1H), δ7.9 (m, 1H),. MS APCI, m/z = 603(M^+). LC/MS 2.13 Min.

The amine component, (2,3-*cis*)-3-amino-5-(2-dimethylamino)ethyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b) was prepared in the following manner:

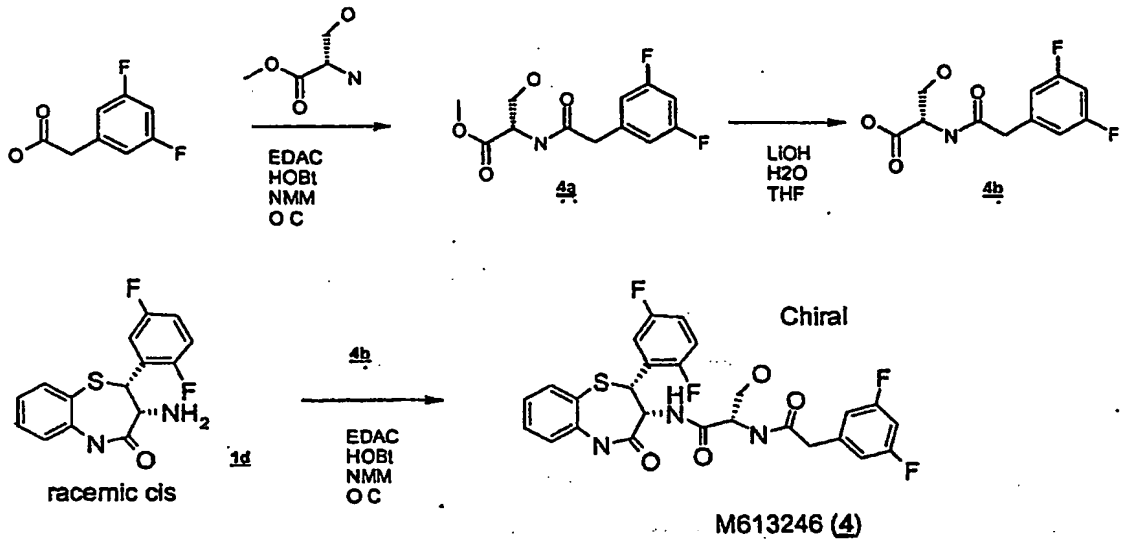
a. **Benzyl (2,3-*cis*)-5-(2-dimethylamino)ethyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (3a)**

To a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 1c (530 mg), prepared as described in Example 1, part c, in methyl isobutyl ketone (14 mL) was added 10N NaOH (0.6mL) followed by H_2O (2.3 mL) and N, N-dimethylaminoethylchloride hydrochloride (260 mg). The reaction mixture was heated to 95° C for 4 H. (HPLC indicated 3:1 3a:1c), allowed to cool to RT and diluted with EtOAc. The organic phase was collected and consecutively washed with H_2O (3X), brine, dried (Na_2SO_4), filtered and the solvent removed in vacuo to yield crude oil. The crude oil was purified by flash chromatography (5%MeOH/$CHCl_3$) to afford pure title compound (400 mg, 60%). ^{1}H NMR (300 MHz, d6-DMSO) δ2.2 (d, 6H), δ2.3 (m, 1H), δ2.4 (m, 1H), δ3.27 (m, 1H), δ3.6,(d of t, 1H), δ4.4 (t, 1H), δ4.5 (t, 1H), δ4.9 (s, 2H), δ5.3 (d, 2H), δ6.8 (d, 1H), δ7.2–7.3 (m, 6H), δ7.4 (t, 1H), δ7.6-7.7 (m, 2H), δ7.76, (d, 1H), δ7.86 (m, 1H). MS APCI, m/z = 512(M^+). LC/MS 2.23 Min.

b. **(2,3-*cis*)-3-amino-5-(dimethylamino)ethyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b).**

Using a method similar to that described in Example 1, part d (Method C), benzyl (2,3-cis)-5-(2-dimethylamino)ethyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate, 3a (90 mg) was converted overnight to crude 3b. The crude product was purified by flash chromatography (5% MeOH, 1% NH_4OH/$CHCl_3$) to afford pure title compound (125 mg, 57%). ^{1}H NMR (300 MHz, d6-DMSO) δ2.29 (s, 6H), δ2.39, (m, 1H), δ2.64,(m, 1H), δ3.62 (m, 1H), δ3.79 (d, 1H), δ4.56 (dt, 1H), δ5.27 (d, 2H), δ6.95–7.05 (m, 2H), δ7.28 (m, 1H), δ7.40 (d, 1H), δ7.72, (d, 1H), δ7.78 (m, 1H). MS APCI, m/z = 378(M^+). LC/MS 1.23 Min.

Example 4. (4)



Example 4. (2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide (4)

To a solution *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b) (75 mg) in DCM (15 mL) at 0°C under N_2, was added racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one-HCl (1d) (100 mg) followed by the HOBt-hydrate (97 mg) and NMM (32 µL). Reaction stirred for 5 Min. and then added EDAC-HCl (84 mg) and NMM (50 µL). The reaction mixture was stirred 2 H at 0°C under N_2, concentrated in vacuo and partitioned between H_2O (100 mL) and EtOAc (125 mL). The organic phase was collected and consecutively washed with H_2O, saturated $NaHCO_3$, brine, dried (Na_2SO_4), filtered and evaporated to yield a mixture of the title compound and (2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide. The crude product (165 mg) was purified by flash chromatography (80% EtOAc/hexanes) to afford the title compound (60 mg, 73%) as a white solid. ^{1}H NMR (300 MHz, d6-DMSO) δ (d, 3H), δ3.48 (s, 2H), δ4.21 (q, 1H), δ4.74,(t, 1H), δ4.85 (bs, 1H), δ5.50 (d, 1H), δ6.93 (d, 2H), δ7.09 (m, 1H), δ7.18-7.35 (m, 4H), δ7.45-7.55 (m, 2H), δ7.71 (t, 2H), δ8.17(d, 1H), δ10.68 (s, 1H). MS APCI, m/z = 548(M^+). LC/MS 2.34 Min.

The starting acid, *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b), was prepared in the following manner:

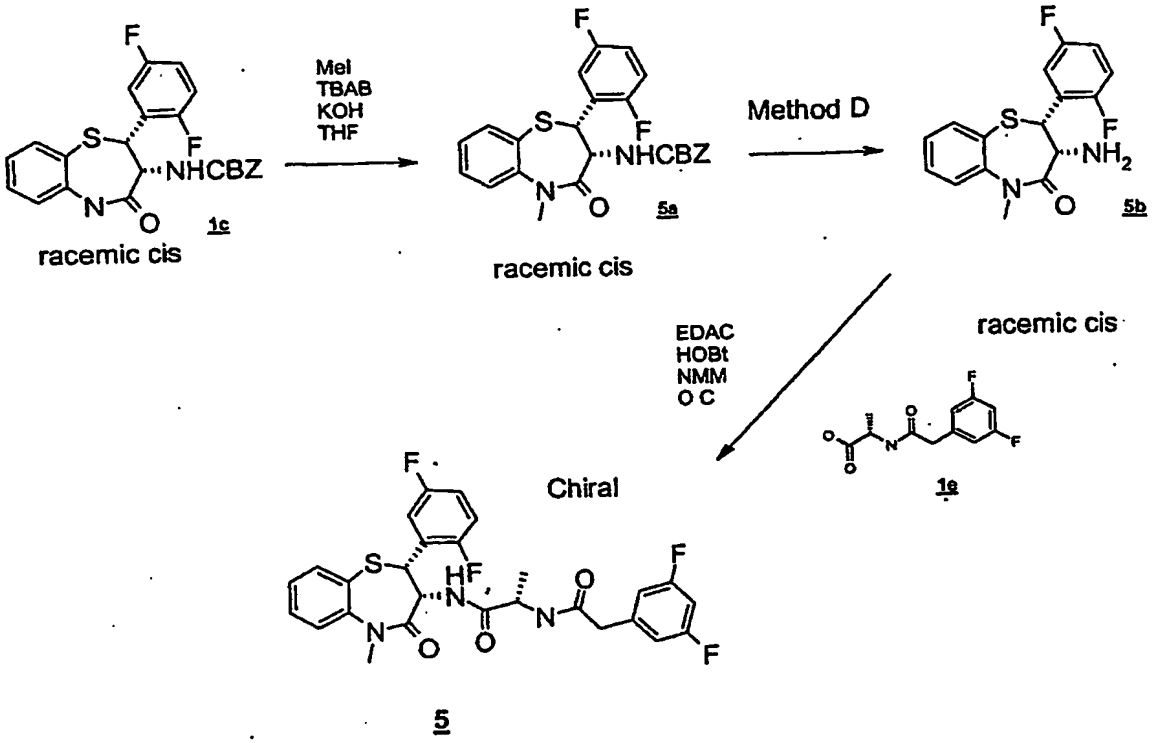
a. *N*-[(3,5-difluorophenyl)acetyl]-L-serine methyl ester (4a)

To an ice cooled solution of 3,5-difluorophenylacetic acid (2.16 g) in anhydrous DCM (100 mL) under N_2 was added HOBt-hydrate (4.23 g), EDAC-HCl (3.6 g), and NMM (2.2 mL). The reaction mixture was stirred at 0°C under N_2 for 15 min and L-serine methyl ester-HCl (1.96g) was added followed by NMM (1.38 mL). The reaction was stirred at 0°C for 1 H and RT for 2 H. The reaction mixture was concentrated in vacuo and partitioned between H_2O (100 mL) and EtOAc (125 mL). The organic phase was collected and consecutively washed with H_2O, dilute $NaHCO_3$, brine, dried (Na_2SO_4), filtered and the solvent removed in vacuo to yield a white solid. Trituration with $CHCl_3$ afforded pure title compound (1.8g). The impure filtrate was subjected to flash chromatography (20% acetone/$CHCl_3$) to afford additional title compound (800 mg, total yield 76%). ^{1}H NMR (300 MHz, d6-DMSO) δ3.57 (d, 2H), δ3.62(s, 3H), δ3.7 (m, 1H), δ4.35,(m, 1H), δ5.1 (bs, 1H), δ7.00 (d, 2H), δ7.09 (t, 1H), δ8.53, (d, 1H). MS APCI, m/z = 274(M^+). LC/MS 1.34 Min.

b. *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b)

To a stirred solution of *N*-[(3,5-difluorophenyl)acetyl]-L-serine methyl ester (4a) in THF (13 mL) was added 1M $LiOH_{aq}$ (13.2 mL) and the mixture stirred at RT for 40 H. Brine (50 mL) was added, the aqueous layer made acidic to pH 1 with 1N HCl (~15 mL), and the aqueous layer extracted with 10%MeOH/ $CHCl_3$ (2X). The organic phase was collected, dried (Na_2SO_4), filtered and the solvent removed in vacuo to afford the title compound (112 mg, 54 %). This material was used without further purification. ^{1}H NMR (300 MHz, d6-DMSO) δ3.57 (d, 2H), δ3.7 (m, 1H), δ4.27,(m, 1H), δ5.03 (bs, 1H), δ7.00 (d, 2H), δ7.09 (t, 1H), δ8.38, (d, 1H). δ12.6, (bs, 1H). MS APCI, m/z = 274(M^+). LC/MS 1.0 Min.

Example 5. (5)



Example 5 N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide (5)

Using a procedure similar to that described in Example 1, except using racemic (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b) (170 mg) as the amine component, the title compound (5) was obtained as a white solid (85 mg, 59%) ^{1}H NMR (300 MHz, $CDCl_3$) δ1.19 (d, 3H), δ3.48 (s, 2H), δ3.50 (s, 3H), δ4.22 (m, 1H), δ4.83,(t, 1H), δ5.56 (d, 1H), δ5.92 (d, 1H), δ6.37 (d, 1H), δ6.8-6.9 (m, 3H), δ6.9-7.0 (m, 2H), δ7.32 (d, 1H), δ7.4-7.5 (m, 2H), δ7.72 (d, 1H). MS APCI, m/z = 546(M^+). LC/MS 2.67 Min.

The amine component (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b) was prepared in the following manner:

a. Benzyl (2,3-*cis*)-5-(methyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (5a)

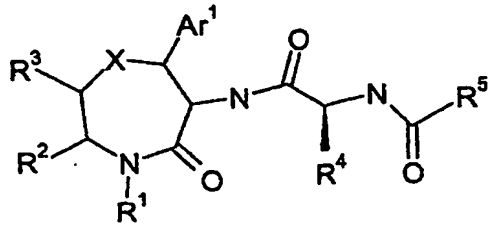
To a round bottom flask charged with powdered KOH (182 mg) under N_2 was added a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 1c (1.1 g) prepared as described in Example 1, part c, in THF (15 mL). To the suspension was added tetrabutylammonium bromide (80 mg) followed by addition of methyl iodide (156 µl) via syringe. The mixture stirred at RT over the weekend. The reaction mixture was partitioned between H_2O and EtOAc. The organic phase was collected and consecutively washed with H_2O and brine, dried (Na_2SO_4), filtered and the solvent removed in vacuo to afford the crude product (1.15 g). Recrystallization from EtOAc (10 mL) yielded pure title compound 5a (660 mg, 58%). ^{1}H NMR (300 MHz, d6-DMSO) δ3.42 (s, 3H), δ4.60 (t, 1H), δ4.93 (s, 2H), δ5.34 (d, 1H), δ7.01 (d, 1H), δ7.22–7.34 (m, 7H), δ7.42 (q, 2H), δ7.62 (s, 1H), δ7.63 (d, 1H), δ7.76 (d, 1H). MS APCI, m/z = 455(M^+). LC/MS 2.93 Min.

b. (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b).

Using a method similar to that described in Example 1, part d (Method D), benzyl (2,3-*cis*)-5-(methyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 5a (600mg) was converted to nearly pure 5b (350 mg, 83%). Recrystallization (ether/hexanes) afforded the pure title compound (162 mg). ^{1}H NMR (300 MHz, d6DMSO) δ1.6-2.5 (bs, 2H), δ3.41 (s, 3H), δ3.50 (s, 3H), δ3.76 (d, 1H), δ5.17 (d, 1H), δ7.25–7.38 (m, 4H), δ7.58 (s, 1H), δ7.59 (d, 1H), δ7.72 (d, 1H). MS APCI, m/z = 321(M^+). LC/MS 1.76 Min.

CLAIMS:

1. A compound of structural diagram (I):



wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 2 sulfur atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, 2 or 3 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5 or 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or substituted phenyl with 0, 1, 2, or 3 R^e;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, C_{1-3}alkoxy, or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, aryl, or heteroaryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, SH, CH_2SCH_3, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, 2 or 3 R^e;

R^{10} is alkyl or R^9;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1,

wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, or NR^aR^b;

R^e is, at each occurrence independently selected from OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-3}alkyl, or C_{1-3}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, or aryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_1-3alkyl, or C_1-3alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, or 2 R^e;

R^{10} is alkyl or R^9;

3. A compound of claim 1,

wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl or aryl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, NO_2, F, Cl, Br, I, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

4. A compound of claim 1,

wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, or 1 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3, C_{1-6}alkyl;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

5. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, or 2 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, NO_2, CF_3, or C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from C_{1-6}alkyl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

6. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

Ar^1 is a 6-membered aromatic or heteroaromatic ring having 0, or 1 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CF_3;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, or CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, or OH;

R^9 is phenyl substituted with 2 R^e;

R^{10} is R^9;

7. A compound of claim 1, wherein X is C, O, SO_2 or S.

8. A compound of claim 1, wherein:

Ar^1 is a 5-or 6-membered aromatic or heteroaromatic ring optionally substituted with 0 or 1 R^e said ring having 1 nitrogen, oxygen or sulfur atom.

9. A compound of claim 1, wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b.

10. A compound of claim 1, wherein:

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl.

11. A compound of claim 1, wherein:

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f.

12. A compound of claim 1, wherein:

R^e is, at each occurrence independently selected from F or Cl.

13. A compound of claim 1, wherein R^f is F or Cl.

14. A compound of claim 1, wherein R^4 is H or CHR^7R^8.

15. A compound of claim 1, wherein R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$.

16. A compound of claim 1, wherein:

R^7 and R^8 are, at each occurrence independently selected from H or OH.

17. A compound of claim 1, wherein R^9 is phenyl substituted with 2 R^e.

18. A compound of claim 1, wherein R^{10} is phenyl substituted with 2 R^e.

19. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b;

R^a and R^b are, at each occurrence independently selected from H,or C_{1-4}alkyl;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0,1 or 2 R^f;

R^e is, at each occurrence F;

R^f is F or Cl;

R^4 is H, or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H or OH;

R^9 is phenyl 3, 5-disubstituted with F;

R^{10} is phenyl 3, 5-disubstituted with F.

20. A compound of formula (I) selected from:

(2S)-N-[(2S,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2S,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3S)-2-(2,5-difluorophenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3S)-2-(2,5-difluorophenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3R)-2-(2,5-difluorophenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2R,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;
N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

(2*S*)-*N*-[(2*S*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2*S*)-*N*-[(2*R*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
pharmaceutical acceptable salt thereof.

A compound according to any one of claims 1 to 21, for use as a medicament.

The use of a compound as defined in any one of claims 1 to 21, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with β-amyloid production, Alzheimer's disease, or Down's Syndrome.

23. A method for the treatment of neurological disorders associated with β-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of claim 1.

24. A method for inhibiting γ-secretase activity comprising administering to a host in need of such inhibition a therapeutically effective amount of a compound of claim 1 that inhibits γ-secretase activity.

25. A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising administering a therapeutically effective amount of a compound as defined in claim 1.

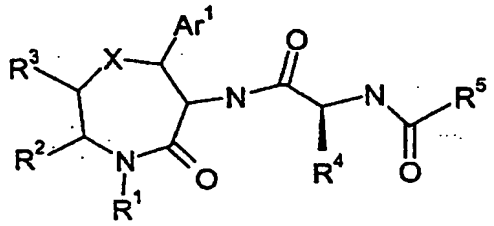
26. A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt as claimed in any one of claims 1 to 21.

27. A pharmaceutical composition comprising a compound of formula (I), as defined in any one of claims 1 to 21, together with at least one pharmaceutically acceptable carrier, diluent or excipent.

ABSTRACT

NOVEL BENZOTHIAZEPINES AND USES THEREOF

This invention relates to novel compounds having the structual diagram (I)



to their pharmaceutical compositions and to their methods of use. These novel compounds inhibit γ secretase and thereby inhibit the production of amyloid β protein, thereby acting to prevent the formation of neurological deposits of amyloid protein. The present invention relates to the treatment of neurological disorders related to amyloid β protein production such as Alzheimer's disease.